THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR BRYXTA 400 (BEVACIZUMAB 400 MG/ 16 ML) CONCENTRATE FOR SOLUTION FOR INTRAVENOUS INFUSION

Version number 1.0
21 August, 2023

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1. Introduction

Bryxta 400 has been developed by Intas as a proposed biosimilar product to the reference medicinal product Avastin of Genentech/Roche having bevacizumab as the active substance. Bryxta 400 is antineoplastic medicine belongs to the pharmacotherapeutic group “monoclonal antibodies” (ATC code: L01XC07). Bevacizumab (Avastin, Genentech/Roche) is a recombinant humanised monoclonal antibody of the immunoglobulin (Ig) G1 class that selectively binds to Vascular endothelial growth factor (VEGF). The binding of bevacizumab to VEGF inhibits the binding of VEGF to its receptors on the surface of endothelial cells, Flt-1 (also known as VEGF receptor-1 [VEGFR-1]) and kinase insert domain receptor (also known as VEGF receptor-2 [VEGFR-2]). Neutralizing the biological activity of VEGF inhibits the formation of new tumour vasculature, causes regression in newly-formed tumour vasculature, and normalises the remaining tumour vasculature, thereby inhibiting tumour growth. Bryxta 400 is approved in Tanzania for use only in adult patients.

1.1 Product details

Registration number	TAN 23 HM 0315
Brand name	Bryxta 400
Generic name, strength and form	Each vial contains; 400mg/16 mL (25mg/mL)
ATC classification	ATC code L01XC07 - antineoplastic agents, other antineoplastic agents, monoclonal antibodies
Distribution category	POM
Country of origin	India
Associated product	Bryxta 100
Marketing Authorization Holder	Cadila Healthcare Limited, Address: Zydus Corporate Park, Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), NR Vaishnodevi Circle, Sarkhej – Gandhinagar – Highway, Ahmedabad – 382 481 India
Local Technical Representative	Pyramid Pharma Limited P.O. Box 16215, Dar es Salaam

1.2 Assessment procedure

The application for registration of Bryxta 400 was submitted on 21/05/2020. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 01/06/2023.

1.3 Information for users

Visual description of the finished product	Colourless to pale brown liquid solution
Primary packing material	5 mL USP Type I glass vial with 20 mm fluorinated polymer - coated butyl rubber stopper and 20 mm flip-off seals
Secondary packing materials	A printed carton box
Shelf-life and storage condition	Unopened Vial: 24 months with storage

	conditions 'Store between 2ºC to 8 ºC. Do not Freeze, Protect from Light' Diluted Solution: Within 24 hours after dilution when stored at temperature between 2 - 8ºC
Route of administration	Intravenous
Therapeutic indications	**Metastatic Colorectal Cancer** Bryxta in combination withfluoropyrimidine–based chemotherapy is indicated for thetreatment of patients withmCRC (metastatic colorectal cancer). **Non-Squamous Non–Small Cell Lung Cancer** Bryxta, in combination with platinum-based chemotherapy is indicated to patients for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamousnon–small cell lung cancer. Bryxta in combination with erlotinib, is indicated to patients for the first-line treatment of unresectable, advanced, recurrent or metastatic non–squamous non–small cell lung cancerbearing EGFR activating mutations. **Glioblastoma** Bryxta is indicated as a single agent therapy for the treatment of glioblastoma with progressive disease in adult patients following prior therapy. **Metastatic Breast Cancer** Bryxta in combination with capecitabine is indicated for the first-line treatment of those metastatic breast cancer patients where other chemotherapy options such as taxanes or anthracyclines are not considered appropriate. This therapy should not be given to those patients who in the prior one year have been given taxanes and anthracyclines in an adjuvant setting. Bryxta in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer patients. **Metastatic Renal Cell Carcinoma** Bryxta in combination with interferon alpha is indicated for the treatment of advanced and/or metastatic renal cell carcinoma. **Persistent, Recurrent, or Metastatic Carcinoma of the Cervix** Bryxta in combination with paclitaxel and cisplatin

	or, alternatively, paclitaxel and topotecan is indicated for the treatment of patients with persistent, recurrent, or metastatic carcinoma of the cervix. **Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer** Bryxta in combination with carboplatin and paclitaxel is indicated for the front-linetreatment of patients with advanced FIGO (International Federation of Gynecology andObstetrics) stages i.e., III B, III C and IV, of epithelial ovarian, fallopian tube or primaryperitoneal cancer.Bryxta in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. Bryxta either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Bryxta as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: Bryxta 400

Composition: Bevacizumab 400 mg in 16 mL (25mg/mL), trehalose dihydrate, mono-sodium dihydrogen phosphate, monohydrate di-sodium hydrogen phosphate anhydrous, polysorbate 20, ortho phosphoric acid, sodium hydroxide, water for injection

Pack size: 1vial

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Unopened Vial: 24 months with storage conditions ‘Store between 2^{o}C to 8 ^{o}C. Do not freeze’

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: To be sold by retail only on the prescription of an Oncologist only, read the package insert before use

The details of the primary pack include:

Brand name and strength: Bryxta 400

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Cadila Healthcare Limited
The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Substance

Information on quality of the active substance was submitted in form of DMF.

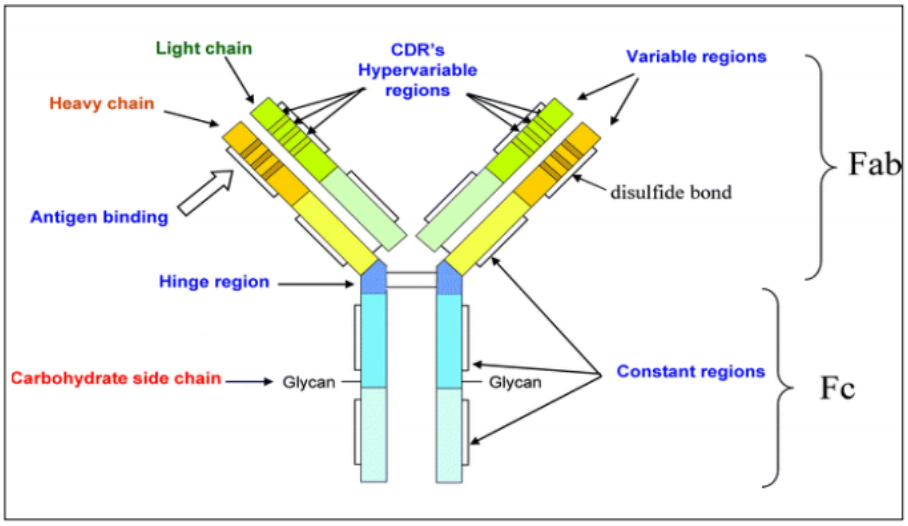
General Information

Bevacizumab active substance is non-compendia.

Molecular formula: $C_{6638}H_{10160}N_{1720}O_{2108}S_4$

Chemical name:
4-Amino-1-(2-deoxy-2,2-difluoro-β-d-erythro-pentofuranosyl) pyrimidin-2(1H)-one hydrochloride

Structure:



Bevacizumab is a humanized IgG1k type of monoclonal antibody. It corresponds to approximately 93% human sequence consisting of constant regions and 7% mouse sequence that forms CDR part. Each of the two light chains is composed of 214 amino acids while each of the heavy chains has 453 amino acid residues. The total molecular weight is approximately 149 kDa. The light and heavy chains are covalently linked by an intra chain disulfide bond; whereas the two heavy chains are linked through two inter chain disulfide bonds. As commonly observed with monoclonal antibodies, bevacizumab also exhibits C- terminal lysine heterogeneity. At asparagine 303 one N-linked glycosylation site is present. The oligosaccharides structures are biantennary with a core fucose and two branches that mainly have terminal zero, one or two galactose (G0, G1 or G2) residues. The predominant glycoform is G0F.

Manufacture

Bevacizumab active substance manufacturer is Cadila Healthcare Ltd.,Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, Sarkhej-Bavla N.H.No.8A,Opp. Ramdev Masala, Village: -Changodar, Tal - Sanand, Dist: Ahmedabad– 382213. India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Food and Drug Control Department-india. Bevacizumab active substance is manufactured by fermentation synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The active substance specifications were set as per in-house standards and ICH guidelines. The parameters monitored during quality control are: appearance, clarity and colour, pH, protein concentration, polypeptide profile, purity,distribution of charged species variants, glycan profile, peptide mapping, relative potency, residual protein – A leachates, host cell-derived contaminating protein, host cell derived contaminating DNA, bacterial endotoxins and osmolarity. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Bevacizumab active substance is 36 months respectively when packed in standard Gamma irradiated cryo-bags (Flexboy® Bag/Celsius bag) of different capacity (0.5 L to 20 L capacity) at the intended storage condition of -25 °C ± 5 °C.

Quality of the Drug Product

Formulation

Bryxta 400 is a colourless to pale brown liquid solution.

Bryxta 400 contains the active substance Bevacizumab and other ingredients listed here after: α, α-Trehalose dihydrate, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, polysorbate 20, water for injections. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The drug product manufacturer is Cadila Healthcare Ltd., Plot Survey No. 23, 25/P, 37, 40/P, 42 to 47, Sarkhej-Bavla N.H.No.8A, Opp. Ramdev Masala, Village - Changodar, Tal - Sanand, Dist: Ahmedabad - 382213 Gujarat state, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

Specifications

The drug product is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: appearance, clarity and colour, pH, protein concentration, polypeptide profile, purity, distribution of charged species variants, glycan profile (2-AB labeled), relative potency, bacterial endotoxins, osmolarity, particulate matter for small volume injections, extractable volume, and sterility. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 (three) batches of the finished product stored at 5±3°C for 24 months and 25°C±2°C for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in 5 mL USP Type I glass vial with 20 mm fluorinated polymer - coated butyl rubber stopper and 20 mm flip-off seals with storage conditions ‘Store between 2ºC to 8 ºC’.

In additional, stability data have been provided demonstrating that the reconstituted solution remains stable for 72 hours when stored at temperature between 2-8ºC.

Safety and efficacy information

Overview of Efficacy

Clinical Trial of CHL's Bevacizumab in Indian Patients

Total 308 subjects were screened to randomized 248 subjects in this trial; 169 subjects in Bevacizumab (Zydus) and 79 subjects in Bevacizumab (Roche). Data of 247 subjects are included in safety analysis; 168 subjects from Bevacizumab (Zydus) and 79 subjects from Bevacizumab (Roche). Total 148 subjects were qualified as per protocol population analysis and 205 subjects qualified as population for efficacy analysis.

Total 148 subjects completed the study; 97 subjects were from Bevacizumab (Zydus) and 51 subjects were from Bevacizumab (Roche). The major reasons for withdrawn included: 30 subject's voluntary request to withdraw, 28 subjects lost to follow-up, 16 subjects due to death, 7 subjects due to AE, 3 subjects due to appearance of concomitant illness making subject unable to continue in the study and 13 subjects due to other reasons.

This study also planned to enroll 40 subjects; 20 in each group, for pharmacokinetic assessment. Total 52 subjects were enrolled in pharmacokinetic assessment; 28 subjects in Bevacizumab (Zydus) and 24 subjects in Bevacizumab (Roche) to have 20 completed subjects in each group for pharmacokinetic assessment after cycle 1. Of which 13 subjects from Bevacizumab (Zydus) and 16 subjects in Bevacizumab (Roche) completed pharmacokinetic assessment after Cycle6.

Criteria for evaluation Primary Efficacy Evaluation:

The primary efficacy variable is Best overall response rate (ORR) in patients with non- small cell lung cancer after cycle 6 (i.e., End of study (visit 11). ORR will be assessed by using response evaluation criteria in solid tumors (RECIST). Best ORR is calculated as the sum of complete response and partial responses (CR+PR) and will be analysed using Chi-Square with Yate's correction.

To establish the equivalence between test and reference products, the 90% confidence interval of the difference in best overall response rate (ORR) between the test and reference at the end of the study (visit 11) for non-small lung cancer must be contain within equivalence limit of (-0.2, 0.2).

Secondary Efficacy Evaluation:
Secondary efficacy variable to compare Pharmacokinetics criteria of bevacizumab following IV infusions of bevacizumab (Test Product, Zydus) and bevacizumab (Reference Product, Roche/Genentech) till Day 22 after cycle 6 with bevacizumab in patients with non-squamous non-small cell lung cancer (NSCLC) after single dose.

Descriptive statistics will be computed and reported for the pharmacokinetic parameters, Cmax, AUC0-t and Tmax.

1) Another secondary endpoint is to demonstrate the safety, tolerability and immunogenicity

of both products. All secondary variables will be analyzed using appropriate statistical methods.

Efficacy summary

The primary endpoint was to compare ORR, the sum of complete response (CR) and partial response (PR) at end of study (Cycle 6, day 127) in Bevacizumab (Zydus) with Bevacizumab (Roche), as assessed by Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

The tumor response evaluation for target lesion in Bevacizumab (Zydus) group was comparable to Bevacizumab (Roche). Majority of subjects had partial response (58.76% vs 62.75%) followed by stable disease (31.96% vs 29.41%) at the end of Cycle 6 (Day 127).

Similarly, the tumor response evaluation for non-target lesion in Bevacizumab (Zydus) and Bevacizumab (Roche) was comparable. Majority of had Non-CR/ Non-PD response (51.55% vs 66.67%) followed by complete response (8.25% vs 9.80%) at the end of study.

Summary of best overall response rate by treatment for per protocol population in Bevacizumab (Zydus) group and Bevacizumab (Roche) group was comparable and majority of subjects showed partial response (60.82% vs 72.55%) followed by stable disease (34.02% vs 27.45%).

The best ORR was 65.98% (64 out of 97 subjects) responders in Bevacizumab (Zydus) group and 72.55% (37 out of 51 subjects) responders in Bevacizumab (Roche)group.

Analysis of Best Overall response rate (ORR) at the EOS (Day 127 ± 3) in per protocol was 65.98% (64 out of 97 subjects) responders in Bevacizumab (Zydus) group and 72.55% (37 out of 51 subjects). There was no statistically significant difference ($p>0.05$) in number of responders for best ORR between test group and reference group. A sample size of 148 subjects was calculated to demonstrate equivalence in best overall response rate at EOS for Bevacizumab (Zydus) versus Bevacizumab (Roche), defined as a 90% confidence interval for the difference of best overall response which fall within the equivalence margin (-19.54, 6.40).

Overview of Safety

Clinical Trial of CHL's Bevacizumab in Indian Patients

Total 308 subjects were screened to randomized 248 subjects in this trial; 169 subjects in Bevacizumab (Zydus) and 79 subjects in Bevacizumab (Roche). Data of 247 subjects are included in safety analysis; 168 subjects from Bevacizumab (Zydus) and 79 subjects from Bevacizumab (Roche). Total 148 subjects were qualified as per protocol population analysis and 205 subjects qualified as population for efficacy analysis.

Total 148 subjects completed the study; 97 subjects were from Bevacizumab (Zydus) and 51 subjects were from Bevacizumab (Roche). The major reasons for withdrawn included: 30 subject's voluntary request to withdraw, 28 subjects lost to follow-up, 16 subjects due to death, 7 subjects due to AE, 3 subjects due to appearance of concomitant illness making subject unable to continue in the study and 13 subjects due to other reasons.

This study was also planned to enroll 40 subjects; 20 in each group, for pharmacokinetic assessment. Total 52 subjects were enrolled in pharmacokinetic assessment; 28 subjects in Bevacizumab (Zydus) and 24 subjects in Bevacizumab (Roche) to have 20 completed subjects in each group for pharmacokinetic assessment after cycle 1. Of which 29 subjects completed

PK assessment after cycle 6; 13 subjects from Bevacizumab (Zydus) and 16 subjects in Bevacizumab (Roche).

Criteria for evaluation Criteria for Safety Evaluation:

1. **Vitals:**

Blood pressure (systolic and diastolic), pulse rate, oral temperature, respiratory rate; Physical examination; body weight; general and systemic clinical examinations i.e., cardiovascular system (CVS), respiratory system (RS), gastro-intestinal system (GI), central nervous system (CNS), musculoskeletal system, reproductivesystem.

2. Laboratory assessment:

- Hematology: Hemaglobin (Hb), hematocrit (Hct), red blood cells (RBC) count, mean corpuscular haemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), packed cell volume (PCV), red blood cell distribution width (RDW-CV), platelet count, CT, BT, PT/INR, white blood cells (WBC) count, absolute neutrophils count, absolute lymphocytes count, absolute eosinophils count, absolute monocytes count, absolute basophils count, smear study (microscopic).
- Liver function test (LFT): Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, proteintest.
- Serum biochemistry includes sodium, potassium, calcium, glucose, Creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein albumin, uricacid.
- Serological tests include testing of HIV, HCV Ab andHbsAg
- Ren
- Urine examination: Physical examination (appearance, colour, specific gravity and pH); Microscopy (epithelial cells, RBCs, pus cells, cast & crystals) and chemical examination(protein).

3. Cardiac function: ECG and2DECHO

4. Adverse Event(s): Frequency of adverse event (s) and severity of adverse events, drop- out due to AEs/SAEs for all subjects will be recorded and reported in the clinical study report as per the DCGIrequirement/CIOMS.

- Causality
- Severity
- Seriousness
- Expectedness

Safety summary

Overall, Bevacizumab (Zydus) and Bevacizumab (Roche) were well tolerated by subjects and comparable in safety profiles.Total 646 AEs were reported in 152 subjects during the study. Of which, 449 AEs experienced by 103 subjects receiving Bevacizumab (Zydus) and 197 AEs experienced by 49 subjects receiving in Bevacizumab (Roche).

There were 432 TEAEs and 42 SAEs reported in Bevacizumab (Zydus) group, and 187 TEAEs and 21 SAEs reported in Bevacizumab (Roche) group. 29 subjects in Bevacizumab (Zydus) group and 13 subjects in Bevacizumab (Roche) group experience at least one SAE during the study. Fourteen subjects died in Bevacizumab (Zydus) and 4 subjects in Bevacizumab (Roche).

Total 24 subjects discontinue due to AE/TEAE/SAE; 18 subjects in Bevacizumab (Zydus), and 6 subjects in Bevacizumab (Roche).

The SOCs with higher number of AEs in Bevacizumab (Zydus) were gastrointestinal disorder, general disorder and administration site condition and Skin and subcutaneous tissue disorders. In Bevacizumab (Roche) the SOCs with higher number of AEs were general disorder and administration site condition, gastrointestinal disorder and Skin and subcutaneous tissue disorders. Commonly reported AEs across the groups were vomiting, asthenia, alopecia, pyrexia, decreased appetite, pain, pain in extremity, paraesthesia, diarrhoea, nausea and cough etc.

Total 619 TEAEs experienced by 150 subjects. Of which, 432 TEAEs reported by 102 subjects in Bevacizumab (Zydus) and 187 TEAEs reported by 48 subjects in Bevacizumab (Roche). Majority of the events were of mild intensity, not related to study drug and recovered/resolved in both the groups.

Total 63 SAEs were reported in 42 subjects during the study. In Bevacizumab (Zydus), 42 SAEs were reported in 29 subjects and in Bevacizumab (Roche), 21 SAEs were reported in 13 subjects. The SOCs with higher number of SAEs were gastrointestinal disorders, general disorders and administration site conditions and infections and infestations. Proportion of SAEs was similar in both thegroups.

Total 18 deaths were reported during the study; 14 in Bevacizumab (Zydus) and 4 in Bevacizumab (Roche). Majority of the SAEs were of severe intensity, not related with study drug and recovered/resolved in both the groups.The changes from baseline in laboratory parameters, vital signs, general and systemic abnormality were comparable for Bevacizumab (Zydus) and Bevacizumab (Roche)

Benefits and Risks Conclusions

Bevacizumab is a glycosylated protein produced by genetically engineered Chinese Hamster Ovary (CHO) cells as a secreted protein. Glycosylation occurs on the F_c portion of heavy-chains.The pharmacotherapeutic group of Bevacizumab is Antineoplastic agents.

Bevacizumab selectively binds with high affinity to all isoforms of circulating human vascular endothelial growth factor (VEGF), a vasculogenesis and angiogenesis regulator that is overexpressed in most human tumors. Bevacizumab neutralizes VEGF mediated regulation of angiogenesis through a steric blocking of the binding of VEGF to its receptor's Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells, thereby blocking the signal transduction and downstream mitogenic and pro-survival events.

CHL has conducted a highly comprehensive characterization of the physicochemical and biological properties of its Bevacizumab product in comparison with the commercial product Bevacizumab (Roche) to establish biosimilarity. These analyses revealed the CHL product to be a close to fingerprint match of the product to originator's product, Bevacizumab(Roche).

After establishing quality biosimilarity to a very high degree, CHL's Bevacizumab was subjected to a panel of animal toxicity studies. These studies confirmed that the drug was well tolerated and comparable to Bevacizumab (Roche) in its toxicity profile complementing the findings of Quality biosimilarity.The final assessment of biosimilarity rests on the demonstration of safety and efficacy in a clinical setting. CHL has conducted a Phase 3 clinical trial in India. The study is titled, "A prospective, randomized, multi-center study to compare the safety, tolerability and efficacyofbevacizumab (ZydusCadila)withbevacizumab(Avastin®)innon-smallcelllung cancer." The clinical trial results indicate that CHL's product is safe, well tolerated and efficacious drug.

The adverse events reported in Phase III clinical trial of CHL's Bevacizumab drug product were same as that reported for Bevacizumab (Roche).Based on the Quality, Non-clinical and Clinical biosimilarity as well as CHL's extensive market experience, several patients are using the Bevacizumab therapy and are benefitting from its use.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. Bryxta 400 is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

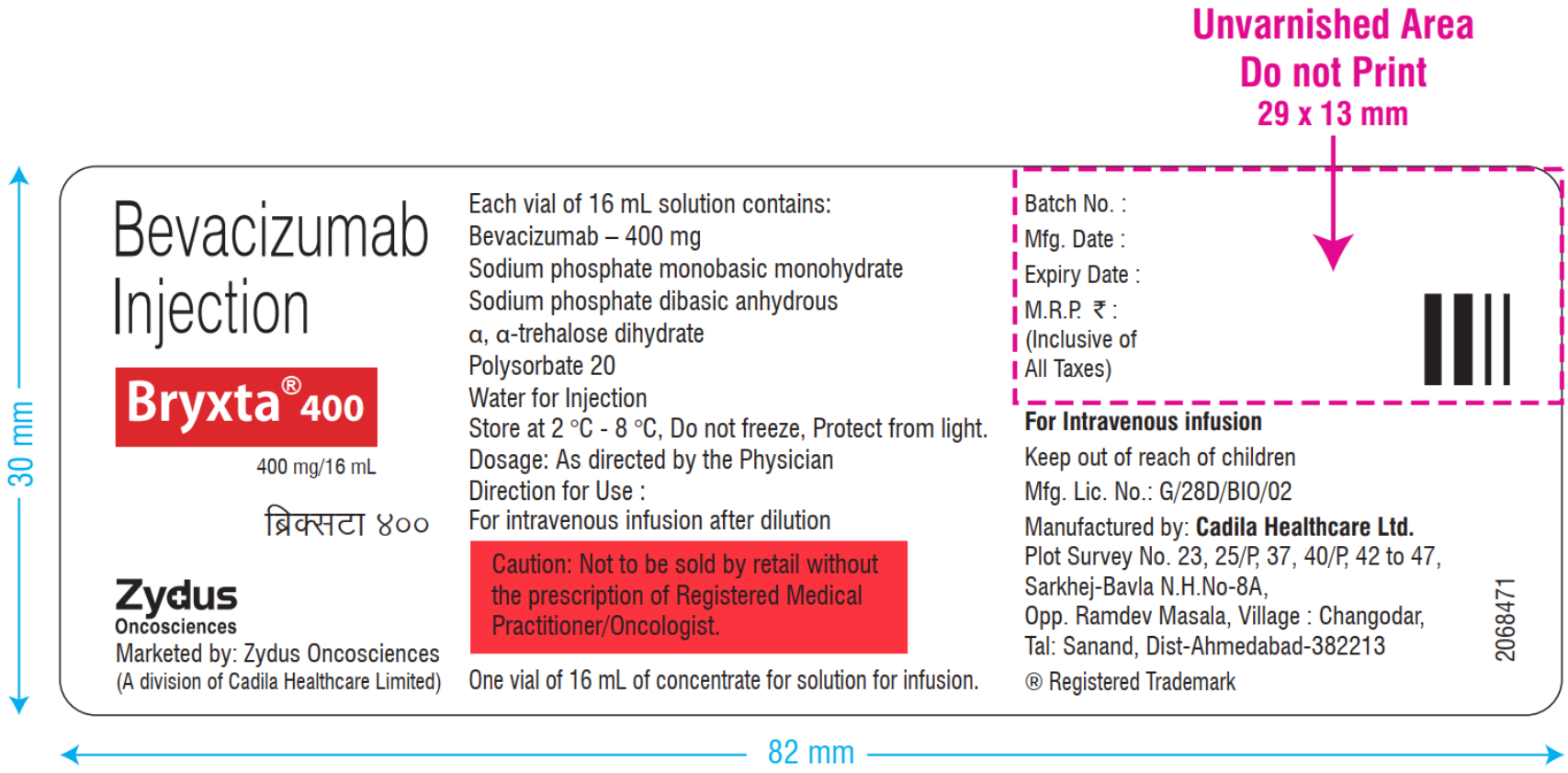
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;



Secondary pack label: